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Published in:
Radiotherapy and Oncology

DOI:
10.1016/j.radonc.2015.07.042

Radiotherapy and Oncology 117 (2015) 139–144

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

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ARTICLE INFO

Article history:
Received 11 January 2015
Received in revised form 27 July 2015
Accepted 29 July 2015
Available online 25 August 2015

Keywords:
Radiotherapy
Head and neck cancer
Swallowing dysfunction
Long-term patterns

ABSTRACT

Objectives: To identify patterns of long-term, radiation-induced swallowing dysfunction after definitive radiotherapy with or without chemotherapy (RT or CHRT) and to determine which factors may explain these patterns over time.

Material and methods: The study population consisted of 238 consecutive head and neck cancer patients treated with RT or CHRT. The primary endpoint was ⩾grade 2 swallowing dysfunction at 6, 12, 18 and 24 months after treatment. Cluster analysis was used to identify different patterns over time. The differences between the mean dose to the swallowing organs at risk for each pattern were determined by using dose maps.

Results: The cluster analysis revealed five patterns of swallowing dysfunction: low persistent, intermediate persistent, severe persistent, transient and progressive. Patients with high dose to the upper pharyngeal, laryngeal and lower pharyngeal region had the highest risk of severe persistent swallowing dysfunction. Transient problems mainly occurred after high dose to the laryngeal and lower pharyngeal regions, combined with moderate dose to the upper pharyngeal region. The progressive pattern was mainly seen after moderate dose to the upper pharyngeal region.

Conclusions: Various patterns of swallowing dysfunction after definitive RT or CHRT can be identified over time. This could reflect different underlying biological processes.

Radiation-induced swallowing dysfunction is a clinically relevant late side effect after definitive radiotherapy (RT) or chemoradiation (CHRT) in patients with head and neck squamous cell carcinoma (HNSCC) which has a substantial impact on health-related quality of life (HRQoL) [1–3]. During and shortly after RT or CHRT, almost all HNSCC patients suffer from a certain degree of swallowing dysfunction. In most cases, acute swallowing dysfunction markedly improves during the first months after treatment. However, 2 years after treatment, many patients still suffer from grade 2 or higher swallowing dysfunction [4–9].

Recently, we reported on a multivariable Normal Tissue Complication Probability (NTCP) model for grade 2–4 swallowing dysfunction at 6 months after definitive RT or CHRT ($SWAL_{M6}$). In that study, the mean dose to the superior pharyngeal constrictor muscle (superior PCM) and the mean dose to the supraglottic larynx were the two most important prognostic factors for $SWAL_{M6}$ [10]. One of the limitations of that study was that the primary endpoint was taken at 6 months after completion of treatment, while other investigators showed that swallowing dysfunction may improve or deteriorate beyond 6 months. Consequently, patients may show various patterns over time [5,6,8,9], which may reflect various underlying radiobiological mechanisms. For instance, swallowing dysfunction at 6 months that gradually decreases during longer follow-up is more likely due to recovering mucositis and laryngeal edema, while progressive swallowing dysfunction after a longer period (e.g. requiring dilatation) is more likely to result from progressive fibrosis. We decided to conduct a prospective cohort study to determine which factors are related to these various patterns. After our first swallowing dysfunction analysis at 6 months, all patients remained included in a standard follow-up program,

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http://dx.doi.org/10.1016/j.radonc.2015.07.042
0167-8140/

which included a subsequent prospective assessment of swallowing dysfunction up to 24 months after completion of treatment.

The purpose of the present study was to identify patterns of long-term, radiation-induced swallowing dysfunction after completion of definitive RT or CHRT and to determine which factors could explain these patterns.

Methods and materials

Patients

The study population of this prospective cohort study consisted of 238 consecutive patients, treated from 1997 at two medical centers in the Netherlands: the VU University Medical Center (VUMC), Amsterdam or the University Medical Center Groningen (UMCG), Groningen. For the purpose of this analysis, we only included the 238 patients with a minimal follow-up of 24 months and a maximum of 1 missing value on swallowing function. We decided to limit the analysis up to 24 months as the number of patients dropped beyond that interval due to end of follow-up or death. All patients were treated with curatively intended conventional three-dimensional conformal RT (3D-CRT) or intensity-modulated RT (IMRT) for HNSCC, either alone or in combination with concomitant chemotherapy. All patients were subjected to a prospective standard follow-up program including assessment of toxicity and HRQoL prior to, during and at regular intervals after treatment [10–12].

Patients who previously underwent surgery, RT or CHRT, who had prior malignancies, and/or distant metastases were excluded. Patients with RTOG grade 2–4 swallowing dysfunction at baseline were also excluded to ensure that the observed swallowing dysfunction was induced by radiation treatment and not by tumor extension. The patient characteristics are listed in Table 1.

Endpoints

The endpoint was defined as the grade of swallowing dysfunction according to the RTOG/EORTC Late Radiation Morbidity Scoring Criteria as assessed at 6, 12, 18 and 24 months after completion of RT or CHRT.

Treatment

Until the end of 2007, the majority of patients were treated with 3D-CRT. Since 2008 patients were mainly treated with IMRT. Regions of interest, RT planning and optimization, and chemotherapy schedules were described previously in more detail [10–12].

All organs at risk (OARs), including the salivary glands, and the swallowing organs at risk (SWOARs), including the superior, middle and inferior PCM, the cricopharyngeal muscle, the esophagus inlet muscle (EIM), the cervical esophagus (CE), the base of tongue (BOT) and the supraglottic and glottic larynx, were delineated as previously described [13,14].

Statistics

In order to classify the patients into patterns of swallowing dysfunction over time, we used a two-step cluster analysis. Cluster analysis creates groups of cases that are homogeneous within themselves, but heterogeneous between each other, based on a predefined set of variables [15–17]. The degree of swallowing dysfunction at baseline and at all subsequent time points (at 6, 12, 18 and 24 months) were considered for cluster modeling based on their contribution to characterizing the patterns of long-term, radiation-induced swallowing dysfunction.

The baseline characteristics for the various pattern groups were then compared on an explorative basis, thus comparing patients with no or minor swallowing dysfunction to the other patterns, using *T*-Test or chi-squared test, whenever appropriate.

For all the SWOARs we produced DVHs for all individual patients. The differences between the mean dose to the SWOARs of each pattern were determined using dose maps. Dose maps are tables with the mean dose for each SWOAR, for each patient grouped per pattern. By using a color scale (from white (lowest D_{mean}) to red (highest D_{mean})) the differences in delivered dose

Table 1
Patient characteristics.

Characteristics		All patients		Low persistent		Moderate persistent		Severe persistent		Transient		Progressive	
		Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Sex	Male	175	74	105	84	25	64	11	58	25	69	9	47
	Female	63	26	20	16	14	36	8	42	11	31	10	53
Age, years	18–65	156	66	76	61	27	69	15	79	27	75	11	58
	>65	82	34	49	39	12	31	4	21	9	25	8	42
Tumor classification	T1–T2	161	68	98	78	25	64	7	37	19	53	12	63
	T3–T4	77	32	27	22	14	36	12	63	17	47	7	37
Node classification	N0	154	65	103	82	24	62	2	11	15	42	10	53
	N+	84	35	22	18	15	38	17	89	21	58	9	47
Primary Site	Larynx	136	57	96	77	20	51	2	11	12	33	6	32
	Oropharynx	71	30	20	16	13	33	11	58	18	50	9	47
	Oral cavity	11	5	4	3	2	5	2	11	1	3	2	11
	Hypopharynx	12	5	3	2	1	3	3	15	4	11	1	5
	Nasopharynx	8	3	2	2	3	8	1	5	1	3	1	5
Treatment modalities	Conventional RT	33	14	21	17	3	8	2	10	4	11	3	16
	Accelerated RT	155	65	93	74	27	69	6	32	19	53	10	53
	Chemoradiation	50	21	11	9	9	23	11	58	13	36	6	31
Radiation technique	3D-CRT	155	65	88	70	19	49	12	63	21	58	15	79
	IMRT	83	35	37	30	20	51	7	37	15	42	4	21
Neck irradiation	No or unilateral	66	28	48	38	9	23	0	0	4	11	5	26
	Bilateral	172	72	77	62	30	77	19	100	32	89	14	74
Baseline swallowing dysfunction (RTOG)	Grade 0	209	88	115	92	32	82	16	84	29	81	17	89
	Grade 1	29	12	10	8	7	18	3	16	7	19	2	11

Abbreviations: RT = radiotherapy, 3D-CRT = three-dimensional conformal RT, IMRT = intensity-modulated RT

between the patterns can be visualized. These dose maps represent the calculated dose based on the initial treatment planning.

We used our previously published multivariable NTCP model for grade 2–4 swallowing dysfunction as the reference model for the current analysis. In that model, the mean dose to the superior PCM and the mean dose to the supraglottic larynx were the two most important prognostic factors [10]. In order to study changes over time, we tested the predictive value of this NTCP model at 6, 12, 18 and 24 months after completion of treatment.

Results

Swallowing dysfunction at different time points

The prevalence of grade 2–4 swallowing dysfunction was 22% at 6 months after RT or CHRT (52 patients), 14% at 12 months (33 patients), 12% at 18 months (29 patients), and 14% at 24 months (33 patients) (Table 2).

Patterns of swallowing dysfunction

With the two-step cluster analysis, we identified five patterns for long-term, radiation-induced swallowing dysfunction within the studied population (Fig. 1):

(1) Low persistent pattern: including those with no or minor swallowing dysfunction during follow-up (125 patients; 53%).
(2) Intermediate persistent pattern: indicating some swallowing dysfunction (grade 1) at 6 months after RT or CHRT which remained more or less unchanged during follow-up (39 patients; 16%).
(3) Severe persistent pattern: defined as swallowing dysfunction ⩾grade 2 at 6 months after RT or CHRT which remained up to two year follow-up (19 patients: 8%).
(4) Transient pattern: including patients with swallowing dysfunction ⩾grade 2 at 6 months after RT or CHRT, that recovered during follow-up (36 patients; 15%).
(5) Progressive pattern: patients with <grade 2 swallowing dysfunction at 6 months after RT or CHRT, which progressed during follow-up to at least grade 2 (19 patients; 8%).

Table 2
Prevalence of swallowing dysfunction at different timepoints.

Variable	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
6 months	41	37	13	8	1
12 months	53	33	8	5	1
18 months	57	31	7	4	1
24 months	62	23	10	4	1

Patient characteristics according to pattern

Of the 238 patients, 74% were males and the mean age was 62 years (range 33–92). The patient characteristics for the various patterns are listed in Table 1. The baseline characteristics were particularly different when patients in the severe persistent pattern group were compared to those in the low persistent pattern group. These patients had higher T-stages and N-stages, had more primary tumors originating from the oropharynx, oral cavity or hypopharynx, were more often treated with CHRT, with bilateral neck irradiation and with conventional RT instead of accelerated RT.

Compared to patients in the low persistent pattern group, patients in the progressive pattern group were more often female, had higher N-stages, and their primary tumors more often originated from the oropharynx or oral cavity.

At six months after treatment patients in the transient pattern group had ⩾grade 2 swallowing dysfunction, compared to grade 1 in the intermediate persistent pattern group. Over the longer term (12–24 months), no difference in swallowing dysfunction was found between these two groups. However, between these two groups no significant differences were found with regard to baseline characteristics.

The progressive pattern group had the lowest percentage of patients treated with IMRT (Table 1), and these patients were on average somewhat older than patients in the other groups.

DVH characteristics according to pattern

To visualize differences in dose distributions across the patterns, dose maps for each pattern group were created, including information on the average D_{mean} to the SWOARs and salivary glands. These structures were grouped according to anatomical location into four main regions, including the upper pharyngeal region (superior PCM, BOT and middle PCM), the lower pharyngeal region (inferior PCM, cricopharyngeal muscle, EIM and CE), the laryngeal region (supraglottic and glottic larynx) and the salivary glands (parotid and submandibular glands).

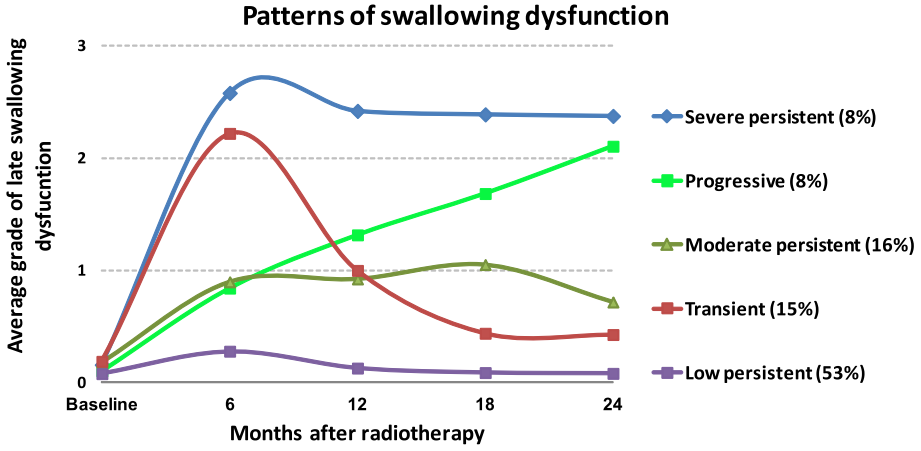

Fig. 1. Patterns of swallowing dysfunction. Percentage of patients in the different patterns: severe persistent = 8%, progressive = 8%, intermediate persistent = 16%, transient = 15% and low persistent = 53%.

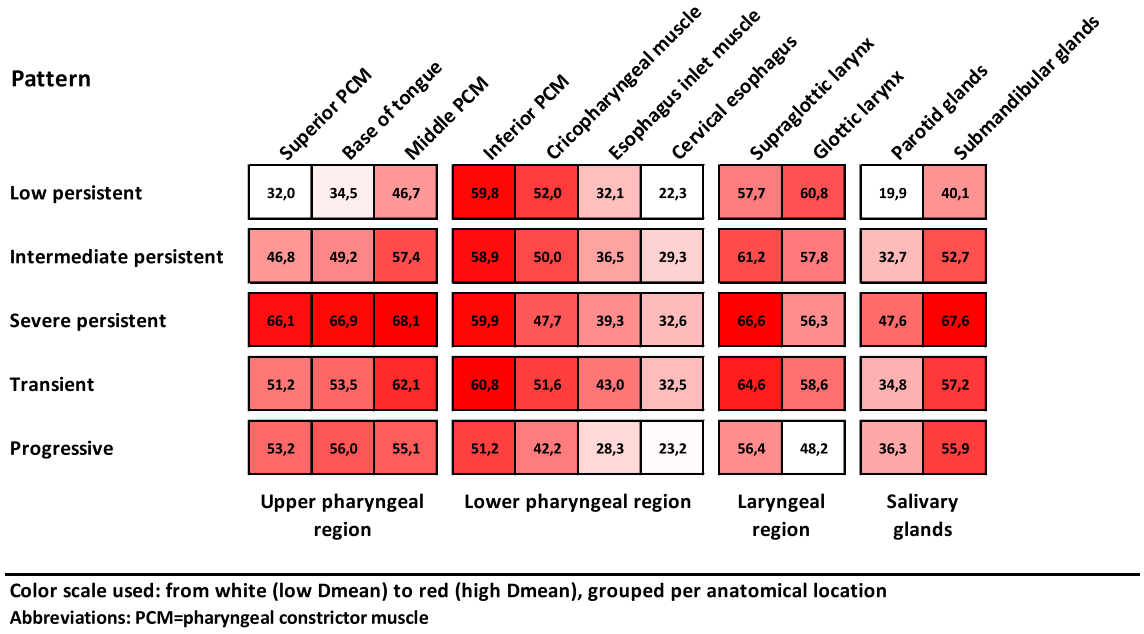

Fig. 2. Average D_{mean} for each pattern group for each organ at risk Color scale used: from white (lowest D_{mean}) to red (highest D_{mean}), grouped per anatomical location. The intensity of the red color corresponds with the level of the mean dose in that specific structure. *Abbreviations:* PCM = pharyngeal constrictor muscle.

From the dose maps, the most important observations were:

(1) Increasing dose levels were observed from the low persistent pattern group to the intermediate persistent and severe persistent pattern groups. Patients in the low persistent pattern group generally received lower mean doses to almost all structures, except to the cricopharyngeal muscle and the glottic larynx. These findings corresponded with the results presented in Table 1, showing that the low persistent pattern group mainly consisted of patients with T1–T2, N0 laryngeal cancers.
(2) The dose maps of patients in the transient pattern group were characterized by high average dose levels to the lower pharyngeal structures and the larynx, combined with lower dose levels to the upper pharyngeal structures and salivary glands, as compared to the severe persistent pattern.
(3) Patients in the progressive pattern group were characterized by the lowest dose levels to the lower pharyngeal and laryngeal structures and higher doses to the upper pharyngeal structures and the salivary glands.

NTCP model for grade 2–4 swallowing dysfunction at 6 months after definitive RT or CHRT

For this subset of 2 year survivors, we tested if the impact of the two independent prognostic factors included in the previously described NTCP model for $SWAL_{M6}$ changed over time. When looking at the odds ratios of the mean dose to the superior PCM and the mean dose to the supraglottic larynx at 6, 12, 18 and 24 months after completion of RT or CHRT, a decreasing contribution of the mean dose to the supraglottic larynx was noted over time, whereas the mean dose to the superior PCM remained more or less stable and was a significant prognostic factor over time (Fig. 2).

Discussion

The purpose of this prospective cohort study was to identify patterns of long-term, radiation-induced swallowing dysfunction after definitive RT or CHRT. The cluster analysis indeed revealed five patterns of swallowing dysfunction over time. Swallowing dysfunction can be persistent (low, intermediate or severe), transient or progressive; we hypothesize that this difference is due to underlying radiobiological mechanisms.

The low persistent pattern group was characterized by relatively high dose levels to the glottic larynx and lower dose levels to the other anatomical structures. This pattern group mainly consisted of patients with early glottic cancer without nodal metastases, treated with small volume irradiation on the primary site only, without elective nodal irradiation (Table 1). Our findings indicate that the combination of these low-risk characteristics explain the relatively low levels of long-term swallowing dysfunction.

The primary endpoint chosen in our study was defined as swallowing dysfunction according to the RTOG/EORTC Late Radiation Morbidity Scoring Criteria as assessed at 6, 12, 18 and 24 months after completion of RT or CHRT. As a consequence, the patterns found in this study only refer to late morbidity according to the RTOG/EORTC. It should be noted that different methods to score swallowing dysfunction using other morbidity scoring systems (e.g. the Common Terminology Criteria for Adverse Events (CTCAE)), or using objective methods such as videofluoroscopy (VF) or Functional Endoscopic Evaluation of Swallowing (FEES), will likely lead to different outcomes and hence might lead to different patterns of long-term swallowing dysfunction [5,7,10]. In the current study, similar swallowing patterns were found for patient-rated swallowing dysfunction.

Compared to patients in the severe persistent pattern group, those in the transient pattern group received similar dose levels to the lower pharyngeal and laryngeal regions, but substantially lower dose levels to the upper pharyngeal region. Thus, higher dose levels to the laryngeal and lower pharyngeal region combined with moderate dose levels to the upper pharyngeal region are more likely to result in transient swallowing dysfunction. In this regard, the results of the current study are in line with the clinical observations of other studies showing laryngeal edema occurring immediately after treatment gradually decreasing over time [2,4,18]. Moreover, a number of investigators found a clear relationship

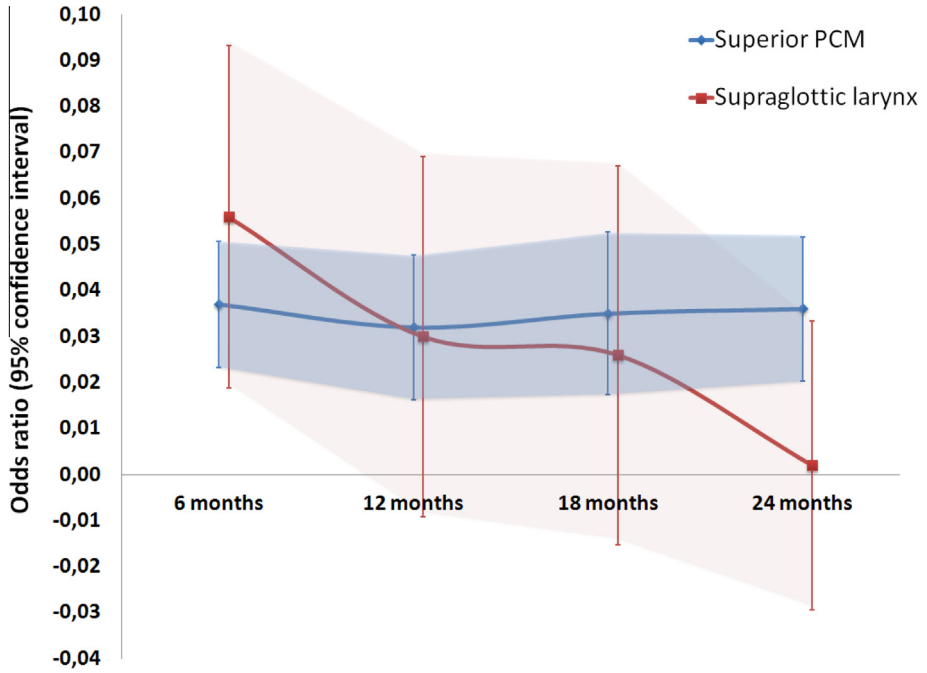

Fig. 3. Effect size (Odds ratio) of the mean dose to the superior PCM and supraglottic larynx on swallowing dysfunction. The effect of the superior PCM remains more or less similar over time, while the effect of the mean supraglottic larynx dose gradually decreases to almost zero at 24 months. *Abbreviations:* PCM = pharyngeal constrictor muscle.

between laryngeal edema and dose to the larynx. If the mean dose to the larynx remains below approximately 44 Gy, edema is generally less profound and more likely to resolve [2,18–21]. Popovtzer et al. [22] found increased muscle thickness in the pharyngeal constrictor muscles on MRI at 3 months after CHRT, especially when the dose to the PCM was above 50 Gy, suggesting that pharyngeal constrictor dysfunction at 3 months after CHRT is mainly caused by inflammation and edema.

It is also interesting to compare the transient with the progressive pattern group. With regard to the dose distributions, the dose to the laryngeal and lower pharyngeal region was much lower in the progressive pattern group. On average, only the dose level to the superior PCM and the BOT was somewhat higher in the progressive pattern group. Based on the dose distributions parameters, it therefore remains unclear which anatomical structure should be considered responsible for the progressive pattern. It should be noted that patients with the progressive pattern were predominantly treated with 3D-CRT instead of IMRT, were somewhat older than the patients in other pattern groups and consisted of relatively more females (Table 1), but it remains unclear whether and to what extent these factors play a role in the patterns of swallowing dysfunction.

When comparing the current study with our previous reported studies [6,10] there is some bias in favor of the node negative patients and patients treated with radiotherapy alone, as the death rates in the first 2 years after treatment were somewhat higher in the advanced cases treated with CHRT.

The pattern groups differed substantially with regard to the dose levels to the salivary glands. A gradual increase in dose to the salivary glands was noted from patients with the low, intermediate and severe persistent pattern. In contrast, the patients in the transient pattern group received much lower doses to the salivary glands than those in the severe persistent pattern group. So far, it remains unclear to what extent xerostomia plays a role in late swallowing dysfunction after RT or CHRT. Other investigators have shown that when the dose to the salivary glands is reduced, while the dose levels to swallowing organs at risk remains the same, the level of swallowing dysfunction also decreased [7,19,23–25]. This suggests that saliva indeed plays a role in lubrication and subsequent swallowing dysfunction. We showed that intermediate persistent cases received higher doses to the salivary glands as well as to the upper pharyngeal swallowing structures as compared to patients with low persistent patterns, suggesting that intermediate persistent swallowing dysfunction may be either due to salivary dysfunction or direct radiation damage to the swallowing structures. Furthermore, it should be noted that in the first year after RT or CHRT, salivary flow and patient rated xerostomia may recover to some extent [24,26–28]. Based on these results, at least part of the recovery from swallowing dysfunction as observed in the transient group could possibly be explained by concomitant recovery of salivary function over time.

Based on the results of the current study, it appears that severe persistent and progressive swallowing dysfunction is mainly related to the anatomical structures in the upper pharyngeal region. These results are supported by the results shown in Fig. 3. In the long-term results, the importance of the dose to the supraglottic larynx appears to decline, while the effect of the dose to the superior PCM remains more or less stable. Therefore, to prevent long-term swallowing dysfunction, we suggest keeping the dose to the superior PCM as low as possible.

New radiation technologies like swallowing sparing IMRT (SW-IMRT) [5,29] might reduce the risk of persistent swallowing dysfunction. Feng et al. [5] found that in patients with oropharyngeal cancer high locoregional tumor control rates can be obtained with IMRT aiming to reduce swallowing dysfunction. It should be noted that these investigators excluded the medial retropharyngeal nodes from the target volume to facilitate sparing of PCM. The SW-IMRT described by Van der Laan et al. [29] is currently being validated in a subsequent cohort study at our institutions. In this regard, swallowing sparing intensity modulated proton therapy (SW-IMPT) [30] is even more promising, as the dose to multiple OARs, including to multiple SWOARs and salivary glands, can be reduced even further.

In conclusion, we identified five patterns of swallowing dysfunction after definitive RT or CHRT. We hypothesize that this difference is due to underlying radiobiological mechanisms of radiation-induced damage and recovery: including (reversible) edema, (slowly progressive) fibrosis, and (recovery of) salivary flow.

Conflict of interest

None.

Acknowledgements

This study was financially supported by a Grant from the Dutch Cancer Society (Grant RUG 2008-3983).

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